6.0 TOXICITY ASSESSMENT

The toxicity assessment portion of the HHRA evaluates the availability of toxicity information for the selected COPCs. The following sections describe the derivation of toxicity benchmarks and the sources that will be used to compile toxicity values for carcinogenic and noncarcinogenic COPCs and chemical warfare agents. The toxicity values proposed for use are presented in Appendix D. Because toxicity values may change as additional toxicity research is conducted, the most current versions of U.S. EPA's Integrated Risk Information System (IRIS) and Health Effects Assessment Summary Tables (HEAST) will be reviewed before completing the final HHRA.

Section 6.1 discusses the toxicity values for the carcinogenic COPCs in the HHRA. Section 6.2 discusses the toxicity values for noncarcinogenic COPCs in the HHRA. Section 6.3 summarizes the toxicity values that will be used to quantify risk from chemical warfare agents. Lastly, Section 6.4 discusses the methodology for calculating toxicity values based on route-to-route extrapolation.

6.1 TOXICITY VALUES FOR CARCINOGENIC COPCS

The toxicity information that will be considered in the assessment of potential carcinogenic risks will include a weight-of-evidence classification and an oral CSF or inhalation unit risk factor (URF). The

weight-of-evidence classification (1) qualitatively describes the likelihood that a chemical is a human carcinogen and (2) is based on an evaluation of the available data from human and animal studies. A chemical may be assigned to one of three groups to indicate its potential for carcinogenic effects: Group A, a known human carcinogen; Group B1 or B2, a probable human carcinogen; and Group C, a possible human carcinogen. Chemicals that cannot be classified as human carcinogens because of a lack of data are categorized in Group D, and chemicals for which there is evidence of noncarcinogenicity in humans are categorized in Group E.

The CSF is defined as the plausible upper-bound estimate of the probability of a response per unit intake of a chemical over a lifetime (U.S. EPA 1989). It is used to calculate an upper-bound probability that an individual will develop cancer as a result of lifetime exposure to a carcinogen. Oral CSFs are derived from studies of carcinogenicity in humans or experimental animals and are typically calculated for chemicals in Groups A, B1, and B2. The oral CSFs are used to assess the dermal pathway in the absence of route-specific dermal CSFs. The inhalation (URF) is defined as the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 microgram per liter (µg/L) in water, or 1 microgram per cubic meter (µg/m^3) in air.

Because toxicity values are updated and revised periodically, the most recent CSFs and URFs were obtained from the following sources in order of preference:

- U.S. EPA. 2000b. IRIS. On-line database: http://www.epa.gov/iris
- U.S. EPA. 1997b. "Health Effects Assessment Summary Tables (HEAST)." Fiscal Year Annual 1997. Office of Solid Waste and Emergency Response. Washington, DC. EPA/540/R-97/036.

If values were not available in IRIS or HEAST, the toxicity values presented in U.S. EPA (1998a) were cited. Additional U.S. EPA documents were also referenced that compile human health risk information obtained from several literature sources. Appendix D summarizes the CSFs and URFs proposed for use in this assessment and their sources. The use of CSFs and URFs to characterize potential carcinogenic health effects is described in Section 7.

6.2 TOXICITY VALUES FOR NONCARCINOGENIC COPCS

The potential for noncarcinogenic health effects as a result of exposure to toxic chemicals will be assessed by comparing an exposure estimate (intake) to an oral RfD or RfC. The RfD represents an average daily oral intake, expressed in milligram per kilogram-day (g/kg-day), which is expected to pose no appreciable risk of adverse health effects to humans (including sensitive populations) during a lifetime of exposure. The RfC represents a continuous inhalation concentration, expressed as milligram per cubic meter (mg/m^3), that is expected to pose no appreciable risk of adverse health effects to humans (including sensitive populations).

An RfD is specific to the chemical and route of exposure (ingestion and dermal contact). For this assessment, oral RfDs will be used to assess dermal exposures in the absence of route-specific dermal RfDs. In addition, RfDs are specific to the duration of exposure. For this assessment, in which exposures are assumed to occur over periods of more than 7 years, only chronic RfDs will be used.

U.S. EPA workgroups review all relevant human and animal studies for each chemical and select the study (or studies) pertinent to the derivation of the specific RfD or RfC. RfDs and RfCs are often derived from a measured or estimated no observed adverse effect level (NOAEL). The NOAEL corresponds to the dose or concentration that can be administered without inducing observable adverse effects. If a NOAEL cannot be determined, the lowest observed adverse effect level (LOAEL) is used. The LOAEL corresponds to the lowest daily dose administered that induces an observable adverse effect. The toxic effect characterized by the LOAEL is referred to as the "critical effect."

NOAELs are most often based on data from experimental studies in animals. Both the experimental parameters and the extrapolation of animal data to humans are potential sources of uncertainty. Hence, in deriving an RfD or RfC, the NOAEL or LOAEL is divided by uncertainty factors to ensure that the RfD or RfC will be protective of human health. The uncertainty factors usually occur in multiples of 10, and each factor represents a specific area of uncertainty inherent in the extrapolation from available data. Uncertainty factors account for (1) extrapolation of data from animals to humans (interspecies extrapolation), (2) variation in human sensitivity to the toxic effects of a compound (intraspecies differences), (3) derivation of a chronic RfD or RfC based on a subchronic rather than a chronic study, and (4) derivation of an RfD or RfC based on a LOAEL instead of a NOAEL. Modifying factors between 0 and 10 may also be applied to accommodate other factors or additional uncertainty associated with the data. For most compounds, the modifying factor is 1.

For this assessment, the primary sources of the chronic RfDs and RfCs for the oral and inhalation exposure routes will be the same as those listed above in Section 6.1 for CSFs and URFs. The RfDs and RfCs proposed for use in this assessment are listed in Appendix D. The use of RfDs and RfCs to characterize potential noncarcinogenic health effects is described in Section 7.

6.3 TOXICITY VALUES FOR CHEMICAL WARFARE AGENTS

U.S. EPA has not developed toxicity values for military-unique chemicals; however, the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) has developed various exposure limits for chemical agents, including general population air values and oral RfDs (USACHPPM 1999). The Centers for Disease Control and Prevention has evaluated public inhalation exposure limits for nerve agents and mustard agents, and the U.S. Army has adopted these inhalation exposure standards. In a 1999 Technical Memorandum prepared by the USACHPPM, entitled "Derivation of Health-Based Environmental Screening Levels for Chemical Warfare Agents," inhalation exposure limits were used as surrogate RfCs. Oral RfDs have been developed for the agents under the sponsorship of the Army Environmental Center at Aberdeen Proving Ground. These values were approved as interim oral RfDs by the Army Office of the Surgeon General in 1996 and have been reviewed by the Subcommittee on Chronic Reference Doses for Selected Chemical Warfare Agents. The USACHPPM is currently evaluating the comments and recommendations prepared by the Subcommittee. The DSHW has reviewed the derivation of the interim oral RfDs proposed by USACHPPM and has accepted the values for interim use in the HHRA pending adoption by U.S. EPA.

The mustard agent, HD, is considered a human carcinogen (USACHPPM 1999). U.S. EPA has developed an inhalation unit risk for HD based on chronic animal vapor exposure data and a relative potency approach based on short-term carcinogenicity studies. The inhalation unit risk factor developed by U.S. EPA can be converted to an oral CSF of 95 $(mg/kg\text{-}day)^{-1}$. There are also several other proposed interim slope factors for HD. Other proposed interim slope factors for HD include:

- 9.5 $(mg/kg\text{-}day)^{-1}$, based on the relative potency Rapid Screening of Hazard using the current BaP slope factor of 7.3 $(mg/kg\text{-}day)^{-1.}$
- 1.6 $(mg/kg\text{-}day)^{-1}$, evaluated using the relative potency and a new slope factor for BaP of 9.5 $(mg/kg\text{-}day)^{-1}$.

- 15.6 $(mg/kg\text{-}day)^{-1}$, results when the new BaP slope factor is applied to the highest RPF for HD.

- 5.0 and 2.6 $(mg/kg\text{-}day)^{-1}$, using linear extrapolations from benchmark doses producing forestomach hyperplasia in rats.

- 5.3 $(mg/kg\text{-}day)^{-1}$, using a method based on maximum tolerated dose.

The USACHPPM recommends using the geometric mean of the slope factors listed above to derive an HD oral slope factor of 7.7 $(mg/kg\text{-}day)^{-1}$ (USACHPPM 1999). The derivation of an HD oral slope factor has undergone review by the Subcommittee on Chronic Reference Doses for Selected Chemical Warfare Agents. The DSHW has reviewed the derivation of the HD oral slope factor by the USACHPPM and has accepted the value for interim use in the HHRA.

The oral CSFs and RfDs, and inhalation URFs and RfCs proposed for estimating the carcinogenic and noncarcinogenic effects of GB, VX, and HD are presented in Table 6-1.

6.4 TOXICITY VALUES CALCULATED BASED ON ROUTE-TO-ROUTE EXTRAPOLATION

U.S. EPA-recommended toxicity values are always preferred for use in a HHRA, but are not always available. IRIS has withdrawn toxicity values for some compounds in order to review the basis of the values or update the value based on more recent research. In cases such as this, where toxicity benchmarks exist for one route but not the other, and evidence exists that toxicity could occur via the route of exposure without a toxicity value, a toxicity value can be calculated. In such cases, for this protocol, the health benchmarks were calculated based on available U.S. EPA-derived benchmarks values. For instance, if the RfD (mg/kg/day) was available and the RfC (mg/m^3) was not, the RfC was calculated by multiplying the RfD by an average human inhalation rate of 20 m^3/day and dividing by the average human body weight of 70 kg. This conversion is based on a route-to-route extrapolation, which assumes that the toxicity of the given chemical is equivalent over all routes of exposure.

TABLE 6-1

TOXICITY VALUES FOR CHEMICAL WARFARE AGENTS PROPOSED FOR USE IN THE TOCDF HHRA

Agent	Oral RfD[a] (mg/kg-day)	Oral Slope Factor (mg/kg-day)$^{-1}$	Inhalation Unit Risk (:g/m^3)	General Public Exposure Limit (mg/m^3)	Inhalation RfD[b] (mg/kg-d)
HD	7.0-E-06	7.7E+00	8.5E-02	1.0E-04	3.0E-05
GB	2.0E-05	--	--	3.0E-06	9.0E-07
VX	6.0E-07	--	--	3.0E-07	9.0E-08

Notes:

GB	Isopropyl methylphosphonofluoridate
HD	Di-2-chloroethylsulfide
HHRA	Human health risk assessment
kg	Kilogram
mg/kg-day	Milligram per kilogram per day
(mg/kg-day)$^{-1}$	Per milligram per kilogram per day
mg/m^3	Milligram per cubic meter
RfD	Reference dose
TOCDF	Tooele Chemical Agent Disposal Facility
(:g/m^3)$^{-1}$	Per microgram per cubic meter
USACHPPM	U.S. Army Center for Health Promotion and Preventive Medicine
VX	O-ethyl-S-[2-diiospropylaminoethyl]-methyl phosphonothiolate

[a] Oral RfDs are recommended in USACHPPM 1999 based on a Department of the Army memorandum entitled, "Interim Chronic Toxicological Criteria for Chemical Warfare Compounds" from June 4, 1996.

[b] Estimated from the General Public Air Exposure Limits using an inhalation rate of 20 m^3/day and a body weight of 70 kg.

Source: USACHPPM 1999.

The following methodology was used to calculate toxicity values based on route-to-route extrapolation:

1) Oral RfDs presented in IRIS-, HEAST-, or U.S. EPA-reviewed documents were used if available. Missing oral RfDs were calculated from the RfC assuming route-to-route extrapolation using the following equation:

$$Oral\ RfD = \frac{RfC * 20\ m^3/d}{70\ kg\ BW} \qquad \text{Equation 6-1}$$

2) Oral CSFs presented in IRIS/Heast/EPA reviewed documents were used when available. In the case of missing oral CSFs:

   a) Oral CSF = Inhalation CSF, or

   b) Oral CSF = Inhalation CSF calculated from Inhalation URF assuming route-to-route extrapolation.

3) Inhalation RfCs presented in IRIS/Heast/U.S. EPA reviewed documents were used when available. If RfCs were not available, they were calculated from the RfD assuming route-to-route extrapolation using the following equation:

$$Inhalation\ RfC = \frac{RfD * 70\ kg\ BW}{20\ m^3/d} \qquad \text{Equation 6-2}$$

4) Inhalation RfD values were calculated as follows:

   a) From the inhalation RfC obtained from IRIS/Heast/U.S. EPA reviewed documents using the following equation:

$$Inhalation\ RfD = \frac{RfC * 20 m^3/d}{70 kg\ BW} \qquad \text{Equation 6-3}$$

   b) If the *RfC* was not available from IRIS/Heast/U.S. EPA reviewed documents, the following was assumed:

$$Inhalation\ RfD = Oral\ RfD \qquad \text{Equation 6-4}$$

5) For inhalation URFs, values were obtained from IRIS/Heast/U.S. EPA reviewed documents. If the inhalation URFs were not available, they were calculated from oral CSF, using the following equation:

$$Inhalation\ URF = \frac{Oral\ CSF * 20\ m^3/d}{70\ kg\ BW * 1000\ \mu g/mg} \qquad \text{Equation 6-5}$$

6) The inhalation CSFs presented in IRIS/Heast/U.S. EPA reviewed documents were used when available.

a) If no inhalation CSF was available, it was calculated from inhalation URF, using the following equation:

$$Inhalation\ CSF = \frac{InhalationURF * 70\ kg\ BW}{20\ m^3 / d} * 1000\ \mu g / mg \quad \text{Equation 6-6}$$

b) If no inhalation URF was available, the following was assumed based on route-to-route extrapolation:

$$Inhalation\ CSF = Oral\ CSF \quad \text{Equation 6-7}$$

Route-to-route extrapolation of toxicity values does introduce uncertainty into the risk assessment. By using this method, it must be assumed that the qualitative data supporting the benchmark value for a certain route also applies to the route in question. For example, if an *RfD* is available and the *RfC* is calculated from that value, the risk assessor is assuming that the toxicity seen following oral exposure will be equivalent to toxicity following inhalation exposure. This assumption could overestimate or underestimate the toxicity of the given chemical following inhalation exposure. Because of the degree of uncertainty involved in using toxicity values calculated based on route-to-route extrapolation, a qualitative assessment of the calculated toxicity values used will be included in the uncertainty section of the risk assessment.